Somatostatin-receptor-targeted radionuclide therapy for progressive meningioma: benefit linked to 68Ga-DOTATATE/-TOC uptake

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Abstract: BACKGROUND: The prognosis of patients with progressive meningioma after failure of surgery and radiotherapy is poor. METHODS: We retrospectively evaluated the safety and efficacy of somatostatin-receptor (SSTR)-targeted radionuclide therapy ((177)Lu-DOTATATE [n = 16], (90)Y-DOTATOC [n = 3], or both [n = 1]) in patients with progressive, treatment-refractory meningiomas (5 World Health Organization [WHO] grade I, 7 WHO grade II, 8 WHO grade III) and in part multifocal disease (17 of 20 patients). RESULTS: SSTR radionuclide treatment (median of 3 treatment cycles, median administered dose/cycle 7400 MBq) led to a disease stabilization in 10 of 20 patients for a median time of 17 months. Stratification according to WHO grade showed a median progression-free survival (PFS) of 32.2 months for grade I tumors, 7.2 for grade II, and 2.1 for grade III. PFS at 6 months was 100% for grade I, 57% for grade II, and 0% for grade III. Median overall survival was 17.2 months in WHO grade III patients and not reached for WHO I and II at a median follow-up of 20 months. In the analysis of single meningioma lesions, maximal and mean standardized uptake values in pretherapeutic (68)Ga-DOTATOC/-TATE PET/CT were significantly higher in those lesions with radiographic stability after 6 months. In line with this, high expression of SSTR via immunohistochemistry was associated with PFS >6 months. CONCLUSIONS: SSTR-targeted radionuclide treatment has activity in a subset of patients with meningioma. Expression of SSTR via immunohistochemistry or radionuclide uptake might serve as a predictive biomarker for outcome to facilitate individualized treatment optimization in patients with uni- and multifocal meningiomas.

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Somatostatin-receptor-targeted radionuclide therapy for progressive meningioma - benefit linked to ^{68}Ga-DOTATATE/-TOC uptake

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Conflicts of interest

KS has received honoraria from Roche for advisory board participation. MW has received research grants from Acceleron, Actelion, Alpinia Institute, Bayer, Isarna, MSD, Merck & Co, Novocure, PIQUR and Roche and honoraria for lectures or advisory board participation or consulting from Celldex, Immunocellular Therapeutics, Isarna, Magforce, MSD, Merck & Co, Northwest Biotherapeutics, Novocure, Pfizer, Roche and Teva. JCT has received research grants from Aesculap and BrainLab and honoraria for lectures or advisory board participation or consulting from BrainLab, Celldex, MerckSerono, Roche and Siemens. The other authors declare no conflicts of interest.

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Abstract

Background: The prognosis of patients with progressive meningioma after failure of surgery and radiotherapy is poor.

Methods: We retrospectively evaluated the safety and efficacy of somatostatin-receptor (SSTR)-targeted radionuclide therapy (^{177}Lu-DOTATATE (n=16), ^{90}Y-DOTATOC (n=3), or both (n=1) in patients with progressive, treatment-refractory meningiomas (5 WHO grade I, 7 WHO grade II, 8 WHO grade III) and in part multifocal disease (17 of 20 patients).

Results: SSTR radionuclide treatment (median of 3 treatment cycles, median administered dose/cycle 7,400 MBq) led to a disease stabilization in 10 of 20 patients for a median time of 17 months. Stratification according to WHO grade showed a median progression-free survival (PFS) of 32.2 months for grade I tumors, 7.2 for grade II, and 2.1 for grade III. PFS at 6 months was 100% for grade I, 57% for grade II, and 0% for grade III. Median overall survival was 17.2 months in WHO grade III patients and not reached for WHO I and II at a median follow-up of 20 months. In the analysis of single meningioma lesions, maximal and mean standardized uptake values in pretherapeutic ^{68}Ga-DOTATOC/-TATE-PET/CT were significantly higher in those lesions with radiographic stability after 6 months. In line with this, high expression of SSTR via immunohistochemistry was associated with PFS > 6 months.

Conclusions: SSTR-targeted radionuclide treatment has activity in a subset of patients with meningioma. Expression of SSTR via immunohistochemistry or radionuclide uptake might serve a predictive biomarker for outcome to facilitate individualized treatment optimization in patients with uni- and multifocal meningiomas.

Keywords: Somatostatin receptors, meningioma, radionuclide, PET

Background

Meningiomas are the most common primary brain tumors in the central brain tumor registry of the US (CBTRUS, 2008-2012)[1]. According to the World Health Organization (WHO), meningiomas are classified into grade I (benign meningioma), grade II (atypical meningioma) and grade III (anaplastic meningioma) categories[2]. Surgical resection is the standard of care. Usually, adjuvant treatment is not needed for long-lasting tumor control, particularly in WHO grade I meningiomas. Patients with WHO grade II and grade III meningiomas, especially in case of incomplete resection, commonly receive adjuvant radiotherapy. However, a subgroup of patients, particularly with high grade meningiomas, show highly aggressive tumor growth despite repeated surgical resections and radiotherapy. There is no standard of care beyond surgery and radiotherapy in progressive meningioma. A meta-analysis of 47 publications on medical therapy for progressive meningioma showed that this subgroup of patients exhibits a very poor prognosis: weighted average progression-free survival at 6 months (PFS-6) was 29% for WHO grade I meningioma and 26% for WHO grade II/III meningioma[3]. Radiographic response beyond disease stabilization is rarely reported in these studies with partial response rates below 3% and complete response below 1%[3]. There have been several attempts to treat small cohorts with cytotoxic chemotherapy and targeted therapy; however, these studies largely failed to show substantial therapeutic benefit[4-7]. Some activity was recently attributed to anti-angiogenic agents such as bevacizumab and sunitinib, however, PFS-6 rates still were below 50%[8,9]. Somatostatin receptors (SSTR) overexpressed in meningiomas have been proposed as a therapeutic target for systemic treatment[10]. However, somatostatin analogs have shown only limited efficacy in retrospective series and phase II studies[11-13]. DOTA-D-Phe1-Tyr3-octreotide (DOTATOC) and DOTA-D-Phe1-Tyr3-octreotate (DOTATATE) are agents with a chelator-site (DOTA) and a binding site to somatostatin receptors (octreotide and octreotate, respectively). It is feasible to label the

chelator site with β^+ emitting gallium-68 (^{68}Ga) for PET diagnostic purposes or with β^- emitting radioisotopes yttrium-90 (^{90}Y) and lutetium-177 (^{177}Lu) for therapeutic purposes. The therapeutic radionuclides deliver SSTR-targeted β^--radiation within a few millimeters distance of the binding site[14,15], in contrast to biochemical receptor interference as proposed for somatostatin analogs (e.g., octreotide, pasireotide). Radionuclides binding to SSTR have shown efficacy in neuroendocrine tumors[16]; however, little is known about the efficacy of this treatment for SSTR-positive meningiomas especially in highly pretreated populations[17-21]. We here studied the safety and efficacy of SSTR-based radionuclide therapy for patients with meningiomas that progressed after several lines of therapy. In addition, we analyzed whether the intensity of SSTR expression or tracer uptake in the pretherapeutic ^{68}Ga-DOTATATE/-TOC positron emission tomography (PET) scans are associated with therapeutic efficacy.

Patients and methods

Patients and histology

We reviewed the clinical records of 20 consecutive meningioma patients who underwent SSTR-based radionuclide therapy for progressive disease between 2009 and 2015 at the University Hospital of Zurich (n=11, 3 of them were sent to the University Hospital of Basel for radionuclide treatment) and the University Hospital of Munich (n=9). Approval for the retrospective analysis was obtained from the local ethics committees or was not required according to local regulations. Histological grading and histological subtyping of the most recent available histological samples were performed at the sites according to the WHO classification 2007[2]. The time interval between resection of lesions and radionuclide therapy varied between 1 and 97 months (median 13 months). SSTR-type-2 (SSTR-2) expression assessed by immunohistochemistry was available in 18 of 20 patients. Deparaffinized tissue sections were immunostained for SSTR-2 (SS-800, Gramsch Laboratories, Schwabhausen,

Germany) followed by nuclear counterstaining with Mayer hemalaun. SSTR-2 expression was scored as grade 1 (no/weak), grade 2 (mild/modest), grade 3 (moderate) and grade 4 (strong) by board-certified neuropathologists (ER, US); representative images are shown in Supplementary Figure 1.

Treatment

Radionuclide therapy was delivered with the somatostatin analog DOTATATE labeled with ^{177}Lu (n=16) or DOTATOC labeled with ^{90}Y (n=3), or both (n=1), depending on local availability. Treatment was administered intravenously in cycles of minimal 3,400 MBq and maximal 7,648 MBq per cycle for a maximum of 4 cycles. Co-therapeutic agents commonly included steroids, antiemetics and infusion of solutions containing 0.25% lysine/arginine for renal protection in line with previous studies evaluating SSTR-based radionuclide therapy[16,17].

Toxicity

The assessment of adverse events related to radionuclide therapy was restricted to the period from the beginning of treatment until 3 months after the last cycle. Data were collected retrospectively using Common Terminology Criteria (CTC) for Adverse Events (version 4.0).

Radionuclide imaging

Patients received pretherapeutic PET/CT with ^{68}Ga-DOTATATE/-TOC (n=17) or indium-111(^{111}In)-octreotide scintigraphy (n=3), confirming the expression of SSTRs prior to therapy. Acquisition of imaging data was performed according to current local conventions and infrastructure. ^{111}In-octreotide scintigraphy was performed to qualitatively document pretherapeutic receptor expression but was not suitable for quantitative analysis. Quantitative lesion-specific analysis of uptake characteristics was done for those patients with available ^{68}Ga-DOTATATE/-TOC-PET-CT scans. The intensity of uptake in single and multiple (visually separate) meningiomas was characterized by maximal and mean standardized uptake value (SUV_{max} and SUV_{mean}) on ^{68}Ga-DOTATATE/-TOC PET/CT by a board-certified

nuclear medicine physician. For analysis of these parameters, a semi-automatic volume of interest (VOI) was drawn using a threshold of 2.3, which was previously shown to discriminate meningioma from tumor-free tissue[22]. In the case of tracer uptake below a threshold of 2.3, SUV_{max} was assessed automatically by using an autocontour VOI. To account for differences in imaging parameters depending on local acquisition procedures, analyses were done both pooled and separately for the centers.

Assessment of response and survival

Since there is no consensus on response criteria for meningioma, we adapted the Macdonald criteria for malignant glioma to assess the response[23]. In brief, bidimensional measurements were performed on Gadolinium-enhancing areas of T1-weighted MRI images for 16 of 20 patients. In 4 patients, contrast-enhanced high resolution CT images were used depending on imaging availability. MRI or CT scans were available with a median of 1.1 months prior to therapy and the next subsequent imaging with a median of 3.8 months after the first cycle of radionuclide treatment. Complete response was defined by complete disappearance of the tumor and partial response by a more than 50% reduction of tumor size. Stable disease was recorded when there was less than 50% decrease or up to 25% increase in size at least 4 weeks after initiation of treatment. Progressive disease was defined either by an increase of more than 25% of tumor size, the appearance of new lesions, clinical decline or death. In subjects with multiple lesions, progression in any of the lesions of more than 25% or increase of total tumor load of more than 25% was considered as progression.

Where applicable, depending on the quality of available digital MRI, tumor load was additionally measured by 3-D-volumetric analysis with PMOD software Version 3.4 (PMOD Technologies, Zurich, Switzerland). The baseline MRI as reference for the relative change of tumor volume was defined as the last MRI before radionuclide treatment. The pre- and posttherapeutic growth rate was estimated using Microsoft Excel 2010 (Redmont, WA, USA)

and defined as the slope of a linear regression trend line of the percentage of pre- and posttherapeutic tumor volumes in relation to the baseline tumor volume (variable y) and corresponding days before and after radionuclide treatment (variable x). In the case of surgical resection or embolization during the interval of volumetric analysis, data points were analyzed separately before and after the interventions.

Statistics

Progression-free survival (PFS) and overall survival (OS) rates were calculated from the first dose of radionuclide until progression and death, respectively. Five patients did not show any tumor progression and 13 patients were alive before the cut-off date (31st of March 2015). These patients were censored at the last date of contact. For the calculation of PFS at 6 months (PFS-6) and OS at 12 months (OS-12), a single patient was excluded due to insufficient follow-up. For the additional lesion-based analysis, the calculation of the progression-free time interval of each single meningioma lesion was performed analogous to the patient-based analysis.

Kaplan-Meier estimation was applied for the calculation of median PFS, median duration of best response, OS and median follow-up. Non-parametric statistics were applied using Spearman correlation coefficient, Mann-Whitney-test and binary logistic regression analysis where indicated (GraphPad Prism software version 5.0 (San Diego, CA, USA), SPSS software version 22 (Ehningen, Germany).

Results

Study population and pretreatment characteristics

Patient and pretreatment characteristics are summarized in Table 1, with individual patient characteristics provided in Supplementary Table 1. A total of 20 patients were identified, with

11 patients initially diagnosed with WHO grade I meningioma and 9 patients with WHO grade II meningioma. The histological grade of recurrent tumors was higher prior to radionuclide therapy in 10 patients and lower in 1 patient, with overall 5 WHO grade I, 7 WHO grade II and 8 WHO grade III meningiomas. The most common histological meningioma subtype at diagnosis was meningothelial (n=8) and prior to radionuclide therapy atypical (n=6). Prior to radionuclide therapy, all patients had documented radiographic progression. Eighty-five percent of the patients had multiple intracranial meningiomas and 20% had extracranial disease. All but one patient underwent repeated surgery with a median number of 3 surgical resections and 40% of patients had been previously treated with at least one embolization. All but 2 patients had previously received radiotherapy for meningioma including one line of radiotherapy in 11 patients, 2 lines in 5 patients and 3 in 2 patients. Beyond conventional radiotherapy, stereotactic radiotherapy was applied in 4 patients and stereotactic radiosurgery (Gamma Knife) in 2 patients (Supplementary Table 1).

The median time of radiotherapy to SSTR based radionuclide therapy was 2.9 years (range 1.3-14.3 years). Four patients were treated with radiotherapy due to preexisting conditions prior to the diagnosis of meningioma; 30% had received at least one line of chemotherapy. Agents used included hydroxyurea, long-acting somatostatin analogs, sorafenib or bevacizumab, alone or in combination with etoposide or doxorubicin. The median time from diagnosis to the start of radionuclide treatment was 10 years.

Treatment

Eighteen patients were treated with radionuclide therapy alone, and 2 patients received combination treatment. One patient with WHO grade II meningioma underwent embolization immediately prior to radionuclide treatment. One patient with WHO grade III meningioma received interferon-α-2a in addition as de-novo combination treatment (Supplementary Table

1). The median number of treatment cycles was 3 with a median single dose of 7,400 MBq and median cumulative dose of 20,153 MBq (interquartile range 13,665-27,593 MBq).

Toxicity

Radionuclide monotherapy was generally well tolerated. Adverse events as assessable retrospectively are summarized in Supplementary Table 2. Lymphocytopenia affected 70% of patients, including severe lymphocytopenia in 30% of patients (25% grade 3, 5% grade 4, 15% persistent grade 3/4 lymphocytopenia). The severity of lymphocytopenia correlated with the number of previous systemic chemotherapic agents (Spearman correlation r=0.56, p=0.01).

Response and outcome

Table 2 and Figure 1 summarize data on response, PFS and OS. None of the patients achieved complete or partial response as assessed by modified Macdonald criteria. In 50% of patients, radionuclide treatment led to stable disease. The median duration of disease stabilization was 17 months. All patients with WHO grade I meningioma responded with stable disease, while the percentage was lower in WHO grade II (57%) or WHO grade III (13%) meningioma. In 4 of 17 patients with multiple lesions, we observed variable intraindividual tumor responses. Median PFS was 5.4 months for all patients pooled (Figure 1A). PFS was not significantly different between WHO I and WHO II meningiomas, in contrast to WHO I and WHO III as well as WHO II and WHO III meningiomas ($p<0.05$, log-rank/Mantel-Cox test, Figure 1B). Median OS for all patients was not reached with a median follow-up of 20 months (Figure 1C). For patients with WHO grade III meningioma, median OS was 17.2 months. Statistically significant differences between WHO grades were not reached with the limitation of 13 censored, i.e., living subjects at time of analysis (Figure 1D).

In addition to formal response assessment, we quantified tumor growth rate by 3-D volumetric analysis in a subset of 8 patients, tabulated in Supplementary Table 1. Two patients with WHO grade I, 1 with WHO grade II, and 5 with WHO grade III tumors had appropriate digital MRI documentation available. Figure 2 confirms progressive tumor growth before radionuclide therapy in these patients. Growth rate was reduced by 25% or more after radionuclide therapy in 4 of 8 patients. Patients lacking a reduction of growth rate by 25% or more or with accelerated growth suffered from WHO grade II (1 patient) or WHO grade III meningioma (3 patients).

In a previous patient-based analysis, high SSTR radionuclide uptake as assessed by visual scoring was shown to correlate with survival after SSTR-based radionuclide therapy[17]. We extended this approach and analyzed single meningioma lesions for SUV_{max} and SUV_{mean} and correlated these parameters with therapy failure, i.e. progression within 6 or 12 months as a binary variable, and with PFS as a continuous variable. Higher uptake of radionuclide (SUV_{max} and SUV_{mean}) was associated with longer PFS (Spearman correlation r=0.37, p=0.0003 and r=0.34, p=0.0024 respectively). Progression of single lesions within 6 months or 12 months correlated inversely with higher SUV_{max} and SUV_{mean} (Spearman correlation r=-0.53 for 6 months, r=-0.57, for 12 months and r=-0.51 for 6 and 12 months, $p<0.0001$ respectively). SUV_{max} correlated with SUV_{mean} (Spearman correlation r=0.96, $p<0.0001$).

Single lesion analysis in pretherapeutic PET elicited lower SUV_{max} and SUV_{mean} in lesions that progressed at 6 months, i.e. SUV was higher in stable lesions (Mann-Whitney-test, $p<0.0001$, Figure 3A, B). Similar results were obtained within single centers, however due to low statistical power not reported here.

SUV_{max} and SUV_{mean} were lower in WHO grade III meningiomas compared with WHO grade I or II meningiomas (Mann-Whitney-test, $p<0.001$ and $p<0.05$). However, SUV_{max} or

SUV_{mean} did not significantly differ in WHO grade I and WHO grade II meningiomas (Figure 3C, D).

To investigate the association of SUV with outcome independent of WHO grade, we separately analyzed meningiomas of different WHO grade and performed multivariate regression analysis. Here we assumed that in patients with multiple lesions, the WHO grade of one lesion was representative for all lesions. For WHO grade I meningiomas, none of the lesions progressed over 6 months, thus not permitting this analysis. In WHO grade II meningiomas, SUV_{max} and SUV_{mean} were significantly lower in those lesions that progressed at 6 months (Mann-Whitney-test, $p<0.01$). The same trend was seen for WHO grade III meningiomas, although significance was not reached (Figure 3E, F). Lesion-specific analysis for progression at 12 months (data not shown) was comparable to the analysis of lesions at 6 months (as illustrated in Figure 3).

In multivariate regression analysis, low SUV_{mean} and high WHO grade were independent parameters associated with progression of lesions within 6 months (Binary logistic regression, odds ratio (OR) 0.275, p=0.023, and OR 35.693, p=0.002, respectively).

We next asked whether SSTR expression in tumor tissue (Supplementary Table 1) as assessed by immunohistochemistry correlated with patient outcome. Comparative lesion-specific analysis was not possible in this retrospective study, because, although patients frequently suffered from multiple lesions, most commonly only single lesions were resected. Higher SSTR expression in tumor tissue was associated with stable disease after radionuclide treatment at 6 months (Spearman correlation r=0.50, p=0.04). No patient with grade 1 (no/weak) SSTR expression level (5 of 18 patients, 4 of these 5 patients suffering from WHO grade III meningioma) had stable disease within 6 months. SSTR expression was not correlated to WHO grade (Spearman r=-0.36, p=0.15).

Discussion

This study confirms and extends current knowledge on SSTR-targeted radionuclide therapy (^{177}Lu-DOTATATE/^{90}Y-DOTATOC) for progressive meningiomas, providing evidence that SSTR radionuclide uptake (SUV_{max} and SUV_{mean}) and SSTR immunoexpression could serve as biomarkers for benefit from treatment. On the basis of a lesion-based analysis of SUV and outcome, lesions that are more likely to be stable after SSTR-targeted treatment could be identified. This innovative approach may facilitate optimization of individualized and lesion-tailored therapy in patients with uni- and multifocal meningiomas, especially in treatment refractory situations.

Our cohort consists of heavily pretreated patients after failure of standard therapeutic options receiving systemic therapy for progressive disease. Despite the poor prognosis of patients with progressive meningioma with PFS-6 rates of 29% for WHO grade I and of 26% of WHO grade II and grade III meningiomas in historical controls derived from a meta-analysis of 47 studies[3], radionuclide therapy resulted in disease stabilization in 10 of 20 patients for a median of 17 months. PFS-6 rates of patients with WHO grade I (100%) and grade II tumors (57%) were higher than in these historical controls, in contrast to poor outcome of WHO grade III tumors (0%). All patients had documented progressive tumor growth before initiating radionuclide therapy. This is especially evident in the volumetric analysis, showing a reduction of the growth dynamics in 50% of patients analyzed (Figure 2). Still, differences in PFS, predominantly in patients with lower WHO grade tumors and documented stable disease as best response, may in part reflect the natural course of the disease.

Evidence of SSTR-based radionuclide therapy is still limited. Previous studies, mostly in small and heterogeneous cohorts with limited data on WHO grade, report similar response rates as our study (Table 3). Higher response rates were achieved in one study with a less pretreated patient population[18] and one study lacking an intention-to-treat-analysis[20]. Response assessments were different between the studies, pointing towards a need for standardized response criteria to design clinical trials for comparable results. PFS-6 rate was analyzed in only one trial, showing similar results with 46%[19] versus 42% in our cohort. OS was assessed in 2 of 5 studies. The mean OS of 8.6 years in one cohort[17] is difficult to compare with the median OS of 40 months in another cohort[19] due to different statistic measures. In our study, median OS from radionuclide therapy was not reached at a median follow-up time of 20 months.

In line with previous data, SSTR-based radionuclide therapy was well tolerated. However, the high incidence of lymphocytopenia should be considered, especially with patients receiving additional immunosuppressive medications and who underwent previous cytotoxic chemotherapy. The higher number of grade 3/4 lymphocytopenia compared to previous studies may be either due to pretreatment characteristics with cytotoxic chemotherapy in our study or the lack of detailed analysis of white blood cell differential counts in previous studies.

In contrast to previous studies, we undertook a lesion-specific approach hypothesizing that radionuclide uptake, especially the SUV_{mean}, may represent a lesion-specific biomarker for benefit of treatment with SSTR radionuclides. This is in line with the concept that high tracer uptake in diagnostic PET results in high radiation dose in therapy[24]. Since none of the patients and none of the individual lesions showed a complete or partial response as defined by Macdonald criteria, and since short PFS intervals are difficult to interpret considering the

natural course of the disease, we chose lesion stability or progression at 6 months as a surrogate marker for response to radionuclide therapy and performed subgroup analysis according to different WHO grades. The finding that lesions that failed to progress within 6 months exhibit higher SUV_{max} or SUV_{mean} (Figure 3A, B) may be useful for clinical decision-making in patients with multiple meningiomas, by identifying lesions with a higher or lower probability of response. This observation holds true when analyzed separately for WHO grade II meningiomas; however, it was not evaluable for WHO grade I meningiomas due to the lack of progression over 6 months (Figure 3E, F). For WHO grade III meningiomas, radionuclide uptake may represent a less powerful biomarker for stability of lesions over 6 months, since the respective subgroup analysis failed statistical significance, however, potentially limited due to small sample size (Figure 3E, F). The relatively low radionuclide uptake of WHO grade III meningiomas in our cohort might at least in part contribute to poor PFS-6 in comparison to historical controls[3].

Multivariate analysis in our cohort of PET parameters and outcome measures via logistic regression analysis identified high SUV_{mean} and low WHO grade as independent parameters associated with lesion stability at 6 months. Hence, SUV_{mean} might represent a biomarker with prognostic and/or predictive value identifying lesions likely to respond to SSTR treatment. The hypothesis of SUV_{mean} as a predictive biomarker can be relatively supported by the fact that the intensity of SSTR by immunohistochemistry correlated with PFS at 6 months but not with WHO grade. In the literature, there are few data on SSTR expression and tumor cell proliferation in meningioma. In vitro, both an antiproliferative and a growth stimulatory role were attributed to SSTR expression[25,26]. In a previous study, SUV_{max} and SSTR expression via immunohistochemistry were highly correlated in surgical specimens while SUV_{max} did not correlate with WHO grade[22]. In our data set, SUV_{max} or SUV_{mean} were not significantly different in lesions of WHO grade I or grade II while WHO grade III tumors exhibited lower

SUV_{max} and SUV_{mean} (Figure 3C,D). Another study suggested that meningioma growth correlated with SSTR expression in WHO grade I and II meningiomas as measured with ^{68}Ga-DOTATATE PET but not in grade III meningiomas, pointing towards an escape strategy from SSTR dependence of meningioma growth in de-differentiated meningioma[27].

In conclusion, there is evidence that radionuclide uptake and intensity of SSTR expression might represent predictive biomarkers for benefit of radionuclide treatment. However, due to the lack of prospective clinical data and the relatively low patient numbers in our study, confirmation of this hypothesis and identification of reliable cut-off values of SUV requires a prospective controlled clinical trial with standardized pre- and posttherapeutic Ga^{68}-DOTATATE/-TOC PET-CT.

Based on our findings, we suggest a lesion-based therapeutic concept for tailoring therapeutic options in patients with multiple meningiomas. This approach is supported by our observation that a subgroup of patients showed variable intraindividual tumor responses. Lesions with lower radionuclide uptake should be subjected to surgery or possibly radiotherapy rather than SSTR radionuclide therapy. In contrast, if a target lesion exhibits high radionuclide uptake, SSTR radionuclide therapy might be a more reasonable therapeutic option. In addition, radionuclide therapy could be considered in early disease, prior to a potential malignant progression, since WHO grade III tumors might less likely show a benefit.

A previous study proposed a SUV_{max} of 2.3 as a reliable discriminator between meningioma and tumor-free tissues (90.1% sensitivity, 73.5% specificity, and 89.0% positive predictive value)[22]. In our cohort, a SUV_{max} of less than 2.3 was in some cases, associated with lesion stability but excessive tumor growth in others despite radionuclide therapy. This indicates that a lesion with a SUV_{max} of less than 2.3 might represent tumor-free tissue with the previously reported sensitivity of 90.1%, however might also be active tumor not likely to respond to

SSTR therapy. For the final identification of target lesions with a SUV_{max} of less than 2.3 to be active tumor tissue, surgery may be warranted.

The limitations of this analysis include the fact that SSTR immunolabeling and pretherapeutic PET imaging were not available for the entire patient cohort, the relatively long time interval between histological assessment of SSTR immunolabeling and radionuclide therapy and the assumption that the WHO grade of the resected lesion is representative of the whole tumor load. Other limitations encompass the retrospective study design, the likely underestimation of toxicity common to all retrospective assessments, the difficulty in identifying delayed toxicity attributable to treatment beyond the arbitrarily chosen cutoff of three months, inhomogeneous patient cohort and diagnostic and treatment protocols. Still, despite this obvious heterogeneity in our data set, we identified the link of higher SUV indicating benefit of treatment relatively arguing for a robust association.

In conclusion, there is evidence that SSTR radionuclide therapy has activity in patients with WHO grade I and grade II meningiomas progressing after standard therapy, especially in cases of high SSTR expression as measured by DOTATATE/-TOC PET-CT or immunohistochemistry. However, the efficacy in WHO grade III meningiomas remains uncertain. Further prospective and randomized trial data and standardized response assessments will be needed to optimally evaluate the role of radionuclide therapy as a systemic therapeutic option in meningioma. For validation of the role of SUV_{mean} as a predictive lesion-specific biomarker, a prospective trial based on the radionuclide uptake profile is warranted.

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Figure 1: Progression-free and overall survival

Progression-free survival (PFS) and overall survival (OS) Kaplan Meier curves for all patients pooled (n=20, A and C), and differentiated by WHO grade (B and D)

Figure 2: Volumetric analysis before and after administration of radionuclide therapy

Changes in tumor volume as assessed by MRI volumetric analysis were analyzed before and after radionuclide treatment in 8 patients (A-H). Individual patient characteristics are available in Supplementary Table 1. Growth rate was estimated as the slope of a linear regression trend line of the percentage of tumor volume related to the baseline MRI before the first cycle of radionuclide (variable y) and days before and after radionuclide treatment on day 0 (variable x). Cycles of radionuclide treatment, surgical resections or embolizations during the time intervals of volumetric analysis were depicted with arrows as indicated. Data points for calculation of growth rate before and after the respective interventions were analyzed separately.

Figure 3: Lesion-specific analysis stratified by SUV and WHO grade

Meningioma lesions, progression-free less than 6 months (PF<6) or more than 6 months (PF>6), were compared for SUV_{max} (A) and SUV_{mean} (B). Lesions were grouped according to WHO grade and analyzed for SUV_{max} (C) and SUV_{mean} (D). Meningioma lesions (PF<6 versus PF>6 months) were analyzed separately for WHO grade regarding their SUV_{max} (E) and SUV_{mean} (F). Each circle represents a single meningioma, different colors represent data acquired from different centers. Median and interquartile ranges are shown. Statistical

comparison was done with Mann-Whitney test (*p<0.05, **p<0.001, ***p<0.0001, ns: not significant).

Table 1: Patient and pretreatment characteristics

Meningioma grade	**I**	**II**	**III**
- at diagnosis, n [%]	11 [55%]	9 [45%]	0 [0%]
- at surgery for recurrence, n [%]	5 [25%]	7 [35%]	8 [40%]
Age, median [range]	43 [18-67]		
Gender			
Male, n [%]	9 [45%]		
Female, n [%]	11 [55%]		
Median KPS prior to ^{177}Lu-DOTATATE/^{90}Y-DOTATOC [range]	75 [40-100]		
Multiple meningiomas - at diagnosis, n [%] - prior to radionuclide therapy, n [%]	 4 [20%] 17 [85%]		
Extent of resection at diagnosis			
Complete resection, n [%]	12 [60%]		
Partial resection, n [%]	6 [30%]		
No data available, n [%]	2 [10%]		
Surgical resections prior to ^{177}Lu-DOTATATE/^{90}Y-DOTATOC, median [range]	3 [1-7]		
Surgical resections after ^{177}Lu-DOTATATE/^{90}Y-DOTATOC - number of patients, n [%] - median number of surgeries [range]	 7 [35%] 0 [0-2]		
Angiographic embolizations prior to ^{177}Lu-DOTATATE/^{90}Y-DOTATOC - number of patients, n [%]	 8 [40%]		
Radiotherapy for meningioma prior to ^{177}Lu-DOTATATE/^{90}Y-DOTATOC - number of patients, n [%] - Re-irradiation, n [%]	 18 [90%] 7 [35%]		
Chemotherapy prior to ^{177}Lu-DOTATATE/^{90}Y-DOTATOC - number of patients, n [%]	 6 [30%]		

Table 2: Response assessment and outcome

Meningioma grade prior to ^{177}Lu-DOTATATE/^{90}Y-DOTATOC	I	II	III	Total
Number of patients	n=5	n=7	n=8	n=20
Best response				
Partial response	0%	0%	0%	0%
Stable disease	5 [100%]	4 [57%]	1 [13%]	50%
Progressive disease	0%	3 [43%]	7 [88%]	50%
Median PFS [months]	32.2	7.6	2.1	5.4
PFS-6	100%	57%	0%	42%
Median OS [months]	Not reached	Not reached	17.2	Not reached
OS-12	100%	86%	63%	79%

Table 3: Review of the literature on radionuclide treatment of meningiomas

Trial design	Patients	Radionuclide	Previous treatment	Best response	Definition of SD	Median PFS	PFS-6	OS from recruitment	Intention-to-treat analysis	Ref.
Phase II	Progressive unresectable meningioma, n=34 (5 WHO I, 6 WHO II, 3 WHO III, 20 not available)	^{90}Y-DOTATOC and ^{177}Lu-DOTATOC	74% Surgery 3% RT 33% Chemo	38% SD	<20% increase of tumor volume (RECIST, CT or MRI)	Not available	Not available	8.6 years (mean OS)	Yes	17
Phase II	Progressive (80%) or unresectable (20%) meningioma, 9 WHO I, 2 WHO II, 1 WHO III, 3 without histology	^{90}Y-DOTATOC	66% Surgery 20% RT 7% Chemo	87% SD	<20% increase of tumor volume (RECIST, MRI)	24 months	Not available	Not available	Yes	18
Phase I	SSTR positive tumors, n=3 meningiomas	^{90}Y-DOTATOC	Not available	33% CR, 67% SD	<50% decrease of tumor volume (CT), progression not defined	Not available	Not available	Not available	No, exclusion of patients not receiving 4 cycles	20
Cohort study	SSTR positive recurrent meningiomas, n=29 (14 WHO I, 9 WHO II, 6 WHO III)	^{90}Y-DOTATOC	90% Surgery 62% RT 3.4% Chemo	66% SD	<50% increase or decrease of lesions (SWOG-criteria, MRI)	Not available	46%[1]	40 months (median OS)	Yes	19
Retrospective	SSTR positive meningiomas, n=8 (5 WHO I, 3 WHO II)	^{111}In-Pentetreotide	74% Surgery 13% RT 0% Chemo	25% PR, 63% SD	<50% increase or decrease of lesions (SWOG-criteria, MRI)	Not available	Not available	Not available	Yes	21

Abbreviations: Chemo, chemotherapy; CR, complete response; PFS: Progression-free survival; OS: Overall survival; Ref, Reference; RT, radiotherapy; SD, stable disease; SSTR, somatostatin receptor

[1] Calculated from graph

Supplementary Table 1: Individual patient characteristics

ID	Age[1]	Histological Subtype[1]	WHO[1]	Histological subtype[2]	WHO[2]	Relevant history prior to diagnosis of meningioma	Type of systemic pretreatment for meningioma	Dose(s) (Gy) and types of previous RT for meningioma	SSTR expression[2]	Cycles[3]	Mean dose /cycle (MBq)	Total dose (MBq)	Best Response	PFS	OS	FU	Fig. 2
1	35	Transitional	I	Transitional	I	None	None	-	Grade 4	4	7339	29354	SD	-	-	18	-
2	38	Meningothelial	I	Anaplastic	III	None	None	50 (CRT), 17 (SRT), 17 (SRT)	Grade 2	1	7445	7445	PD	1	2	2	-
3	67	Meningo-thelial	I	Atypical	II	None	None	54 (CRT), 17 (SRT), 50 (CRT)	Grade 4	3	7436	22309	SD	13	14	14	-
4	18	Transitional	I	Atypical	II	CRT (18 Gy) for acute lymphatic leukemia	None	60 (CRT)	Grade 4	4	7425	29699	SD	-	-	17	-
5	62	Atypical	II	Atypical	II	None	None	54 (CRT), 53 (CRT)	Grade 3	4	7443	29711	SD	22	-	31	-
6	61	n/a	I	Rhabdoid	III	None	Hydroxyurea	16.5 (SRS), 54 (CRT)	Grade 1	2	7383	14765	PD	2	4	4	-
7	31	Meningothelial	II	Atypical	II	Neurofibromatosis type II, 60CoRT (dose n/a) for pilocytic astrocytoma (at age of 6 years)	None	54 (CRT)	Grade 1	3	7419	22257	PD	6	-	20	-
8	34	n/a	I	n/a	III	None	None	54 (fSRT), 54 (fSRT)	n/a	4	7429	29715	PD	5	-	15	-
9	26	Fibroblastic	I	Fibroblastic	I	CRT (dose n/a) for acute lymphatic leukemia (at age of 7 years)	None	54 (CRT)	Grade 4	4	7443	29772	SD	-	-	12	-
10[4]	44	Atypical	II	Atypical	II	None	Hydroxyurea Sandostatin LAR, Bevacizumab	63 (CRT)	Grade 2	2	6660	13320	SD	8	19	19	C

ID	Age[1]	Histological Subtype[1]	WHO[1]	Histological subtype[2]	WHO[2]	Relevant history prior to diagnosis of meningioma	Type of systemic pretreatment for meningioma	Dose(s) (Gy) and types of previous RT for meningioma	SSTR expression[2]	Cycles [3]	Mean dose /cycle (MBq)	Total dose (MBq)	Best Response	PFS	OS	FU	Fig. 2
							+/- Doxorubicin Bevacizumab +Etoposid										
11[5]	33	Atypical	II	Anaplastic	III	None	Bevacizumab +Etoposid	59 (CRT)	Grade 1	3	6968	20905	SD	3	10	10	D
12	54	Meningothelial	I	Anaplastic	III	None	Sandostatin LAR	58 (CRT)	Grade 4	2	6475	12950	PD	2	17	17	H
13	35	Meningothelial	I	Anaplastic	III	None	None	60 (CRT)	Grade 4	1	3400	3400	PD	1	-	27	F
14	49	Meningothelial	I	Meningothelial	I	None	None	54 (CRT)	Grade 3	2	7400	14800	SD	21	-	22	B
15	62	Clear cell	II	Clear cell	II	None	Sorafenib	53 (CRT) 3x10 (SRS)	Grade 3	1	7400	7400	PD	2	3	3	-
16	56	Meningothelial	I	Meningothelial	I	None	None	54 (CRT)	Grade 2	4	5473	21890	SD	-	-	43	A
17	41	Meningothelial	II	Atypical	II	RT (dose n/a) due to retinoblastoma (at age of 3 months)	None	-	n/a	3	6467	19400	PD	4	-	24	-
18	58	Atypical	II	Anaplastic	III	None	None	60 (CRT)	Grade 1	2	7400	14800	PD	2	-	14	G
19	65	Atypical	II	Rhabdoid	III	None	None	63 (CRT)	Grade 1	2	7350	14700	PD	4	-	13	E
20	29	Atypical	II	Transitional	I	None	None	50 (SRT+CRT), 50 (SRT+CRT)	Grade 2	3	7400	22200	SD	-	-	5	-

[1]At time of diagnosis, [2]At time of last surgery before radionuclide therapy, [3]Cycles of DOTATATE or DOTATOC radionuclide treatment, [4]This patient received interferon-alpha-2a during DOTATOC radionuclide treatment, [5]This patient received embolization immediately prior DOTATOC radionuclide treatment

Abbreviations: 60CoRT, Cobalt-60 radiotherapy; CRT, conventional radiotherapy; ID, identification number, Fig, Figure; FU, Follow-up in months; OS, overall survival in months; PFS: Progression-free survival in months; n/a, not available; RT: radiotherapy; SRS, stereotactic radiosurgery; (f)SRT, stereotactic radiotherapy; SSTR, somatostatin receptor; WHO, World Health Organization grade;

Supplementary Table 2: Toxicity[1]

	CTC grade				**Total**
	1	**2**	**3**	**4**	
Hematologic					
Anemia	10%	5%	-	-	10%
Thrombocytopenia	10%	-	5%[3]	-	5%
Lymphocytopenia	25%	15%	25%	5%	70%
Non-hematologic					
Creatinine increase	-	-	-	-	0%
Fatigue	5%	-	-	-	5%
Alopecia	5%	-	-	-	5%
Pituitary insufficiency	-	5%	-	-	5%
Wound complication	-	-	5%	-	5%
Increase of GGT[2]	5%	5%	-	-	10%

[1]Analysis for the time period of treatment, e.g. from the first day of treatment until 3 months after the last treatment

[2]Gamma-glutamyl-transpeptidase

[3]Probably not related to radionuclide therapy

Supplementary Figure 1: Representative SSTR2 immunostains

Representative images for scoring of SSTR expression according to immunohistochemical methods: Grade 1 (no/weak, A), grade 2 (milde/modest, B), grade 3 (moderate, C) and grade 4 (strong, D) expression. Scale bar in A corresponds to 100 µm in A-D.

Figure 1

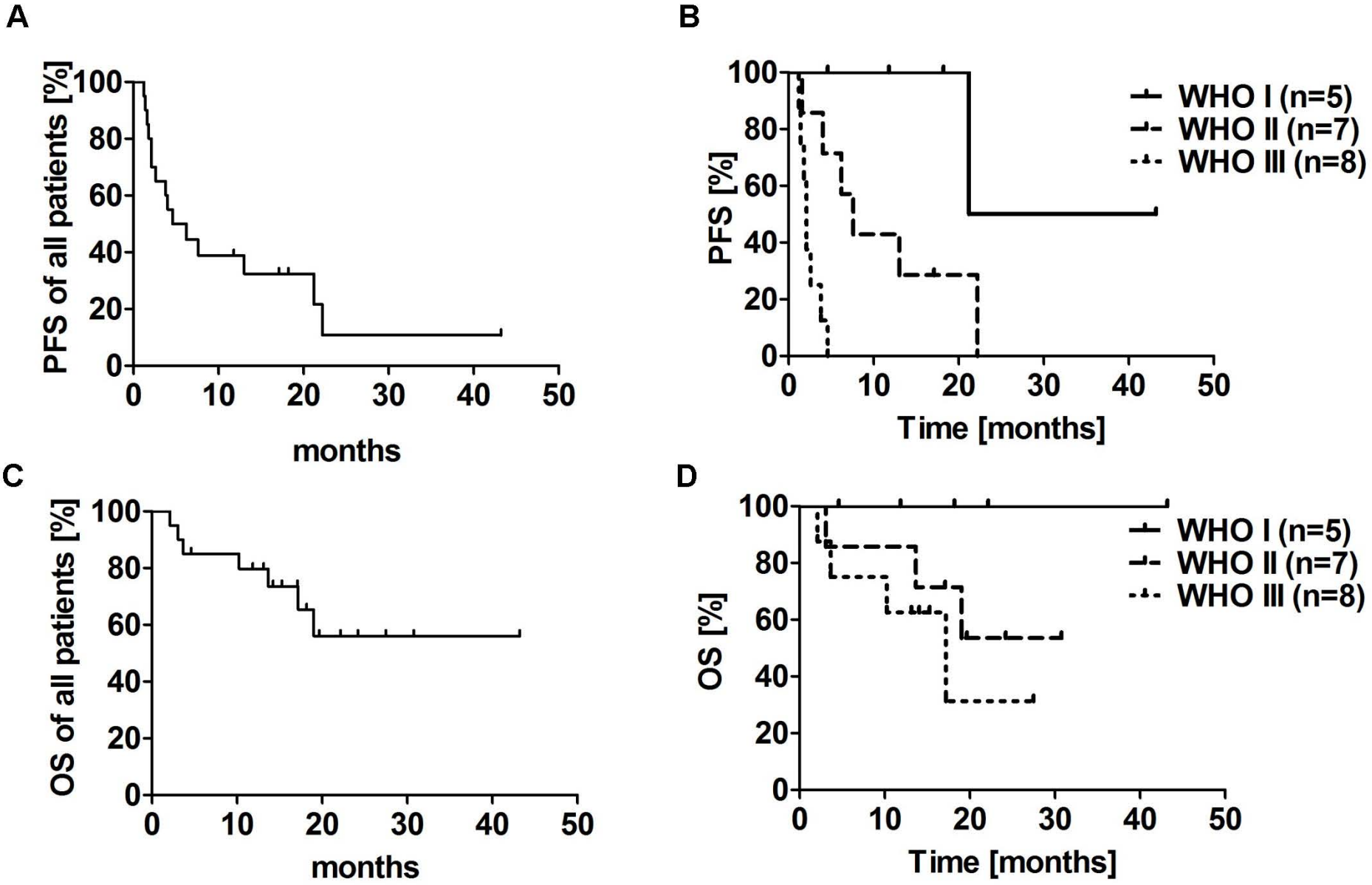

A
PFS of all patients [%]
100
80
60
40
20
0
0
10
20
30
40
50
months
B
PFS [%]
Time [months]
WHO I (n=5)
WHO II (n=7)
WHO III (n=8)
C
OS of all patients [%]
months
D
OS [%]
Time [months]

Figure 2

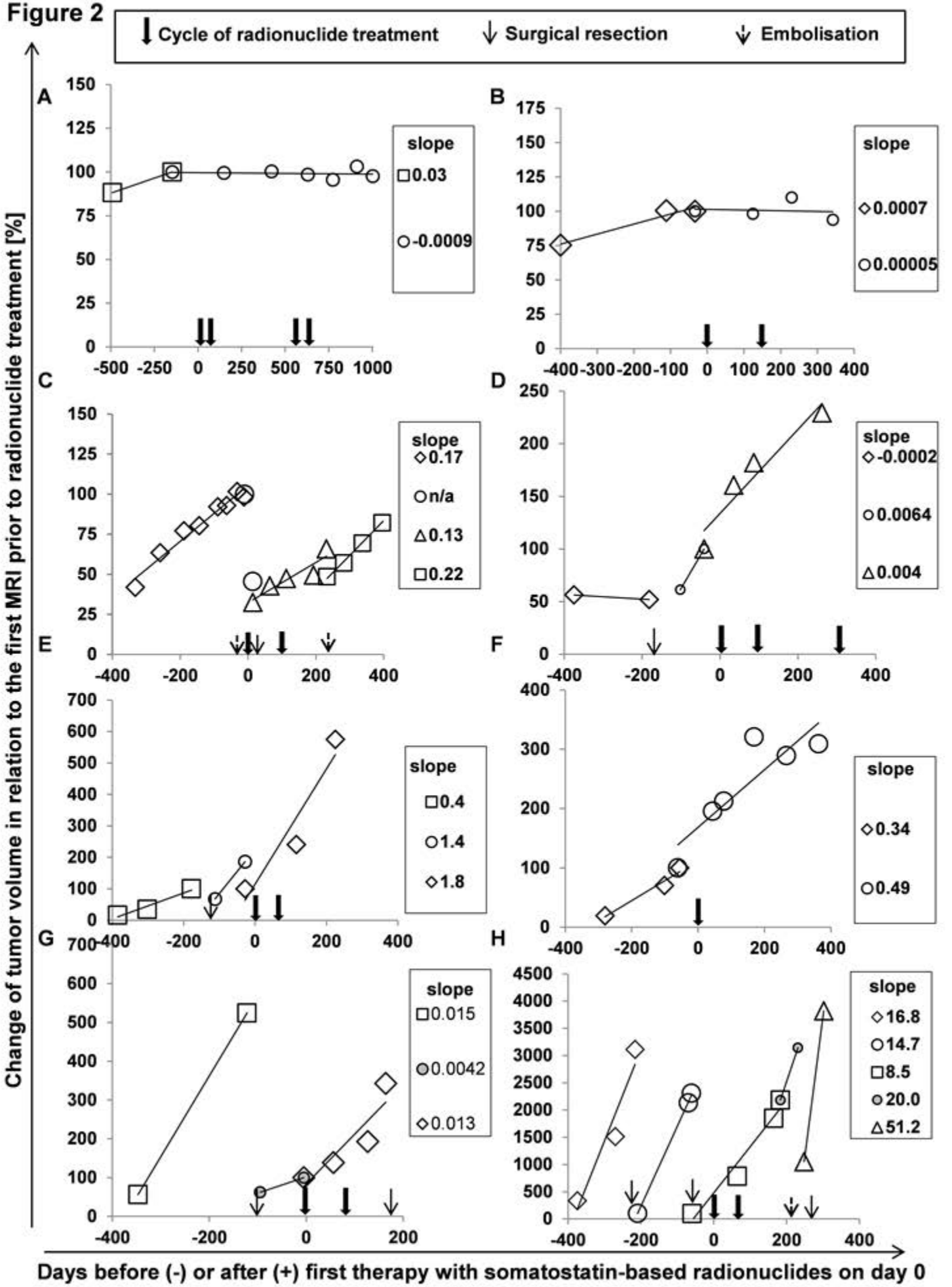
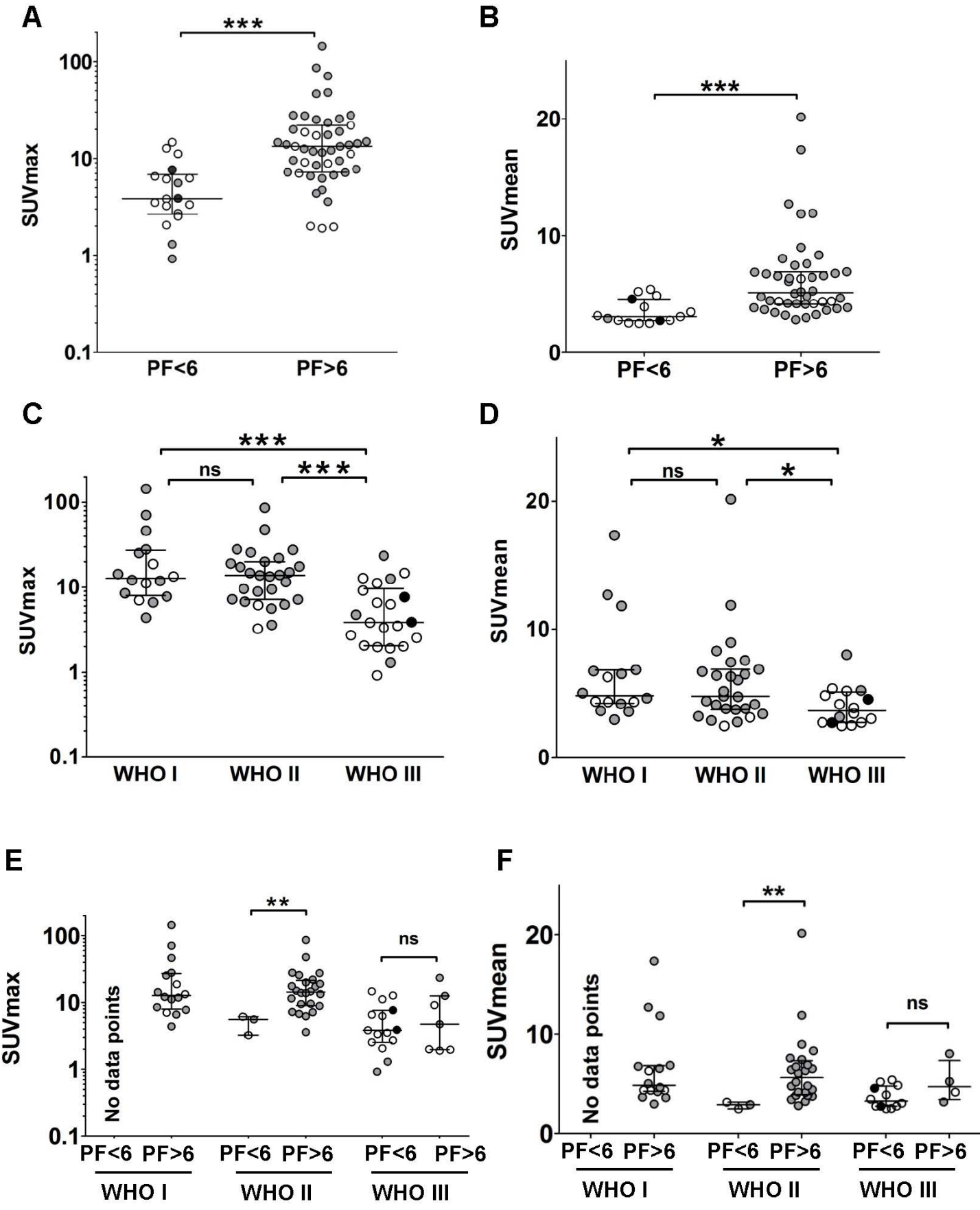

Cycle of radionuclide treatment
Surgical resection
Embolisation
A
slope
0.03
-0.0009
B
slope
0.0007
0.00005
C
slope
0.17
n/a
0.13
0.22
D
slope
-0.0002
0.0064
0.004
E
slope
0.4
1.4
1.8
F
slope
0.34
0.49
G
slope
0.015
0.0042
0.013
H
slope
16.8
14.7
8.5
20.0
51.2
Change of tumor volume in relation to the first MRI prior to radionuclide treatment [%]
Days before (-) or after (+) first therapy with somatostatin-based radionuclides on day 0

Figure 3


A
***
SUVmax
100
10
1
0.1
PF<6
PF>6
B
***
SUVmean
20
10
0
PF<6
PF>6
C
***
ns
***
SUVmax
100
10
1
0.1
WHO I
WHO II
WHO III
D
*
ns
*
SUVmean
20
10
0
WHO I
WHO II
WHO III
E
**
ns
SUVmax
100
10
1
0.1
No data points
PF<6 PF>6
PF<6 PF>6
PF<6 PF>6
WHO I
WHO II
WHO III
F
**
ns
SUVmean
20
10
0
No data points
PF<6 PF>6
PF<6 PF>6
PF<6 PF>6
WHO I
WHO II
WHO III

Supplementary Figure 1